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ABSTRACT

To evaluate whether conceptional or chronologic age should be used to determine scores in developmental follow-up studies, a study was made of 236 normal and 66 neurologically abnormal infants who were similar with respect to conceptional age but different with respect to degree of prematurity. Assessments of possible differences in cognitive and motor performance were made with the Bayley Scales of Infant Development and a neurological examination, which were administered to all babies at 9 and 18 months conceptional age. Infants were divided into four age groups to reflect differing degrees of prematurity: gestational age less than or equal to 32 weeks, 33 to 34 weeks, 35 to 36 weeks, and equal to or greater than 37 weeks. Cognitive and motor raw scores did not differ significantly across the prematurity groups for either neurologically normal or abnormal infants at 9 and 18 months conceptional age, despite differing chronologic ages. Compromised developmental function was detected as indicated by differences between neurologically normal and abnormal babies, especially in the more premature groups. It is concluded that the use of conceptional age as opposed to chronologic age at 9 and 18 months adjusts for "catch-up" due to prematurity, but does not appear to "cover-up" dysfunction. (Author/RH)

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Running Head: Correction for Prematurity

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Abstract

The issue of age adjustment for prematurity was evaluated in 236 normal and 66 neurologically abnormal babies, enrolled in a multicenter NHLBI collaborative study. The Bayley Scales of Infant Development and a neurological examination were administered to all babies at 9 and 18 months conceptional age. Infants were divided into four age groupings to reflect differing degrees of prematurity: gestational age ≤32 weeks, 33 to 34 weeks, 35 to 36 weeks, and ≥37 weeks. Cognitive and motor raw scores did not differ significantly across the prematurity groups for either neurologically normal or abnormal infants at 9 and 18 months conceptional age, despite differing chronologic ages. Compromised developmental function was still detected as indicated by differences between neurologically normal and abnormal babies, especially in the more premature groups. The use of conceptional age as opposed to chronologic age at 9 and 18 months adjusts for "catch-up" due to prematurity, but does not appear to "cover-up" dysfunction.

Innovations in neonatal care have stimulated increased interest in developmental follow-up to evaluate the efficacy of new medical procedures and to identify infants who are at risk for subsequent developmental delays (1). The correction of developmental indices for prematurity by the use of conceptional age instead of chronologic age is typical in follow-up assessment of preterm infants. However, there is disagreement concerning this practice. Investigators who support the use of corrected scores based on conceptional age (chronologic age minus the number of weeks of prematurity), argue that this method takes into account biologic or maturational "catching-up", and that not adjusting for gestational age yields an underestimation of an infant's level of functional development (2-5). Others, who advocate the use of uncorrected scores based on chronologic age, claim these scores are more predictive of subsequent outcome, and that the use of conceptional age may "cover up" abnormalities, causing investigators to attribute delays to biological immaturity when the delays are due to central nervous system damage (6-9). Given the importance of developmental assessment in the burgeoning follow-up programs, adjustment for prematurity, with the resultant potential alteration of comparison age groups, has important diagnostic and prognostic implications (10-16).

The present study was conducted to evaluate whether conceptional or chronologic age should be used to determine scores in developmental follow-up studies. In this study we assessed whether infants, who were similar with respect to conceptional age but different with respect to degree of prematurity, differed in terms of cognitive and motor performance. Specifically, four groups of infants were compared.

All babies in the four groups were the same conceptional age (9 months for one analysis and 18 months for a second analysis); however, the four groups differed with respect to prematurity (gestational age ≤31 weeks, 32 to 33 weeks, 34 to 36 weeks, and ≥37 weeks). Thus, the four groups of infants also differed with respect to chronologic age in that the more premature groups were older and the less premature groups were younger.

If correction for prematurity were unnecessary, infants in the more premature groups should have higher developmental raw scores, as they have older chronologic ages. This outcome is depicted by line A in Figure 1. Such findings would indicate that development was proceeding with chronologic age in spite of the potential deleterious effects of prematurity. On the other hand, if the correction were needed and it adjusted satisfactorily for prematurity, the developmental raw scores for the four groups should not differ, given that the infants in the four groups are the same conceptional age (prematurity subtracted from chronologic age). This outcome is depicted by line B in Figure 1. An equivalent performance in the four groups would indicate that improved performance expected with chronologic age was offset exactly by the degree of prematurity and that conceptional age is a better indicator of development than chronologic age. In addition, neurologically normal and abnormal babies were compared to determine whether correction for prematurity "covered up" dysfunction or if it enabled differentiation of developmental scores between the two groups.

Insert Figure 1 about here

One of the major strengths of the present study is the large sample size. Data were available for 302 infants at 9 months conceptional age and for 261 infants at 18 months conceptional age, as compared to other studies for which sample size ranged from 40 to 72 (2, 3, 5, 15). Moreover, most studies have simply compared premature vs. term babies and have not separated premature infants into groups based on degree of prematurity (11). Those studies that did use groups representing different degrees of prematurity had very few infants in each group, typically 10 to 20 (3, 8). In addition, in the present study, raw scores as opposed to developmental indices were used. This allowed the direct comparison of the "number of items passed," avoiding additional problems which may have arisen as a result of using age norms, cut-off scores, and deviation quotients.

Method

Subjects

Subjects were enrolled in the National Institutes of Health, National Heart, Lung, and Blood Institute Collaborative Study to evaluate the effectiveness of antenatal dexamethasone administration in the prevention of respiratory distress syndrome (RDS). A detailed description of the subject population and rationale can be found elsewhere (17-19). Briefly, a total of 610 babies were enrolled at one of five participating clinical centers: University of Miami, University of Wisconsin (Madison), University of Manitoba (Winnepeg), University of Tennessee (Memphis), and Northwestern University (Chicago). Of these babies, 53% were male; 45% were white; 44% black, and 11%, "other" (Hispanic, American Indian, Oriental, Eskimo). Fifteen percent of the babies were born at 31 weeks gestational age or less (Dubowitz), 25% at

32 to 33 weeks, 38% at 34 to 36 weeks, and 21% at 37 weeks or greater. Twenty-six percent weighed ≤1500g. at birth and 83% were singletons. Previous analyses revealed no differences in cognitive, motor, or neurologic function between steroid-exposed and control infants; therefore these infants were combined in our analyses (18, 19).

From this subject pool, 236 neurologically normal infants and 66 abnormal babies were given the Bayley Scales of Infant Development (20) at 9 months conceptional age as per the original study protocol; at 18 months conceptional age, 231 normal infants and 30 neurologically abnormal babies were evaluated in a cross-sectional design. The reduction in sample size reflects the fact that 73 infants died from prior to 40 weeks conceptional age to 18 months. Further, there was a 37% drop-out rate over the course of the study, with a total of 169 babies withdrawing from prior to the 40 week examination to 18 months (21). Another 66 infants were excluded because of more stringent selection criteria where infants were included only if the Bayley Scales were administered at the conceptional ages of 9 months ± 2 weeks, or 18 months ± 2 weeks. A demographic description of the current sample is presented in Table 1.

Insert Table 1 about here

Procedure

The Bayley Scales of Infant Development (BSID) and a standardized neurological assessment were administered to all infants at 9 and 18 months conceptional age, as part of the original study protocol (22). The Bayley Scales were administered by developmental psychologists who

were blinded as to results of the infants' neurologic exam; pediatric neurologists performed the neurologic assessments. Quality control across centers was maintained by yearly site visits and periodic data edits at the coordinating center (Research Triangle Institute). Bayley mental and psychomotor raw scores and age adjusted mental (MDI) and psychomotor (PDI) developmental indices were obtained for both neurologically normal and abnormal babies. A diagnosis of abnormal neurological function was made if hemisyndrome, diplegia, tetraplegia/quadriplegia, or dysfunction of a lower motor neurone, dyskinetic, cerebellar, or mixed type was found (19).

Statistical Methods

Initially, a two-way analysis of variance (ANOVA) was performed on each of the four outcome measures: 9 month mental and psychomotor raw scores and 18 month mental and psychomotor raw scores (the precedent for use of raw scores was set in the National Collaborative Perinatal Project (23)). Each ANOVA tested the effect of prematurity (gestational age ≤32 weeks, 33 to 34 weeks, 35 to 36 weeks, vs. ≥37 weeks) and neurological status (normal vs. abnormal) on the respective outcome measure. Simple effects tests were used to assess the effect of prematurity (gestational age) within the neurologically normal and abnormal babies separately and to assess the effect of neurological status between each of the four prematurity groups separately. To control for inflated error rate due to multiple simple effects tests, more conservative ensemble-adjusted p values were computed and are reported for all significant effects (24).

Results

9 Month Cognitive and Motor Raw Scores

The simple effects test indicated no significant differences among the four prematurity groups on mean cognitive raw scores obtained at 9 months conceptional age in neurologically normal babies. Similarly, no significant effect of prematurity was found in neurologically abnormal babies. When neurological status was compared in prematurity groupings, neurologically normal babies had higher mean 9 month cognitive raw scores than did abnormal babies in all four groups; however, the difference was significant in only the ≤32 weeks gestational age group (Table 2).

Insert Table 2 about here

No significant differences were found between the four prematurity groups on motor raw scores obtained at 9 months conceptional age in neurologically normal babies. In neurologically abnormal babies, degree of prematurity was significantly related to the 9 month psychomotor raw score; mean 9 month motor raw scores increased as prematurity decreased. Neurologically normal babies had higher mean 9 month motor raw scores than abnormal babies in all four groups; differences were significant in only the ≤32 and 33 to 34 weeks gestational age groups (Table 2).

18 Month Cognitive and Motor Raw Scores

For both neurologically normal and abnormal babies, the effect of prematurity on cognitive raw scores obtained at 18 months conceptional age was not significant. Neurologically normal babies had higher mean

18 month cognitive raw scores than did abnormal infants in 3 out of 4 groups; the normal babies mean scores were significantly higher in only the ≤32 weeks and 33 to 34 weeks age groups.

The effect of prematurity on 18 month conceptional age motor raw scores was not significant for both neurologically normal and abnormal babies. In all four groups, neurologically normal babies had higher mean 18 month psychomotor raw scores than did abnormals; differences were significant in the ≤32 weeks, 33 to 34 weeks, and ≥37 weeks gestational age groups (Table 2).

Discussion

The results showed no effects of prematurity on either 9 or 18 month cognitive or motor raw scores in both neurologically normal and abnormal infants. The findings demonstrate the need for age adjustment for prematurity at 9 and 18 months and support the concept of maturational "catching-up". The need for correction in motor scores up to 18 months has also been recently demonstrated with the Peabody Developmental Motor Scales (16). The current findings are in agreement with investigations which, based on test scores, suggest the need for the use of conceptional age rather than chronologic age (2, 5), and those studies evaluating the onset of other maturational phenomena such as social smiling in preterm infants (25, 26). In these latter studies, the onset of social smiling was more strongly related to corrected age than to chronologic age.

The findings in regard to "covering up" dysfunction are not as clear. Raw scores distinguished compromised development and did not appear to provide undue benefit or "covering up" because of the use of conceptional age, although there was much overlap between groups. This

lack of "covering up" is evident in the comparison of the obtained mean scores to established Bayley norms and the fact that neurologically abnormal babies had lower mean developmental scores in most comparisons with their neurologically normal counterparts. The differences in cognitive and motor raw scores between neurologically normal and abnormal babies were significant in 7 out of 8 comparisons in the two most premature groups (≤32 and 33 to 34), but in only 1 out of 8 comparisons in the other two groups (Table 2). The lack of effect of neurologic status in the less premature groups may have been due to decreased statistical power resulting from smaller cell sizes in these two groups and the use of more conservative ensemble adjusted p values (three additional comparisons of normal and abnormal babies in these two groups would have been significant with conventional p values). The possibility exists also that the type of neurologic dysfunction was more subtle in the less premature babies; hence the Bayley scores may not have been influenced as much as they would had the neurologic impairment been more severe.

Our results differ from those obtained by Caputo et al (6, 7), perhaps because of methodological reasons: scores were not correlated to other outcome measures in our study, babies were grouped by prematurity, the age cohort differed (Caputo et al obtained their babies from 1965 to 1969), and Caputo et al utilized developmental indices from the Cattel and Gesell, whereas we used raw scores from the Bayley Scales of Infant Development. Our results also did not support the findings of Miller et al (8) who reported that uncorrected developmental quotients (i.e., those based on chronologic age) more readily distinguished abnormal babies than did corrected scores in infants <34 weeks

gestational age. These investigators found 11% of the neurologically abnormal babies had a developmental quotient of <80 at one year, however, the numerical scores may not be comparable, as Miller et al used the Griffiths Scales, and several reports suggest that the Griffiths scores are higher than those obtained with the Bayley in multiply handicapped, delayed infants (27, 28). Further, the Griffiths includes assessment of all skills at each age level, and the test instrument has more subjective scoring criteria than does the Bayley.

In summary, our results are compatible with line B in Figure 1 and support the position that there is a need for the use of conceptional age in the follow-up of infants born prematurely, particularly at 9 and 18 months. However, adjustment values may differ depending upon the infant's gestational age and the age at time of testing (12). The question therefore may not be <u>whether</u> to correct or not, but <u>how</u> best to adjust for prematurity, and how to separate maturational delay from delay due to central nervous system dysfunction. Future studies which report longitudinal, normative data in neurologically intact preterm infants born at various gestational ages are needed.

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Table 1

Demographic Data For Neurologically Normal and Neurologically Abnormal Infants at 9 Months Conceptional Age

	Neurologically Normal Infants		Neurologically Abnormal Infants	
Variable	n	%	n	%
Sex				
Male	129	55	33	51
Female	107	45	32	49
Center				
U. of Wisconsin	24	10	2	3
U. of Manitoba	62	26	9	14
U. of Miami	46	19	5	8
Northwestern U.	11	5	22	34
U. of Tennessee	94	40	27	42
Birth #				
Singleton	212	89	61	94
Multiple Birth	25	11	4	6
Birthweight				
≤1500g.	55	23	32	49
>1500g.	182	77	33	51

(table continues)

Table 1

Demographic Data For Neurologically Normal and Neurologically Abnormal Infants at 9 Months Conceptional Age

	Neurologically Normal Infants		Neurologically Abnormal Infants	
Variable	n	%	n	%
Race				
White	107	34	26	40
Black	105	44	27	42
Other	25	11	12	18
$\bar{x}$ Gestational age	34.5		33.17	
(S.D./Range)	(2.74/27.0-42.0)		(2.58/27.0-39.0)	
$\bar{x}$ Birthweight	2031.77g.		1682.49	
(S.D./Range)	(712/880-4590)		(620/745-3680)	
$\bar{x}$ Percentile weight	34.5		30.27	
(S.D.)	(24.97)		(23.34)	

Table 2

Comparison of Raw Scores by Gestational Age and Neurologic Status

Test	Bayley Standardization Raw Score	Neurological Status	Gestational Age Group ≤32 weeks	33-34 weeks	35-36 weeks	≥37 weeks	p
18 month	125	Normal	124.69±0.86	123.31±1.19	117.79±2.38	121.97±2.31	NS
Cognitive Raw			(n=32)	(n=71)	(n=58)	(n=35)	
Scores		Abnormal	111.75±3.37	102.60±21.11	130.33±3.28	119.00±3.77	NS
			(n=16)	(n=5)	(n=3)	(n=5)	
			p=0.0144	p=0.0084	NS	NS	
18 Month	55	Normal	55.13±0.28	55.65±0.31	55.15±0.38	55.43±0.42	NS
Psychomotor			(n=32)	(n=68)	(n=54)	(n=35)	
Raw Scores		Abnormal	46.88±2.49	44.80±8.73	53.67±1.20	45.00±4.97	NS
			(n=17)	(n=8)	(n=3)	(n=5)	
			p=0.0000	p=0.0000	NS	p=0.0000	

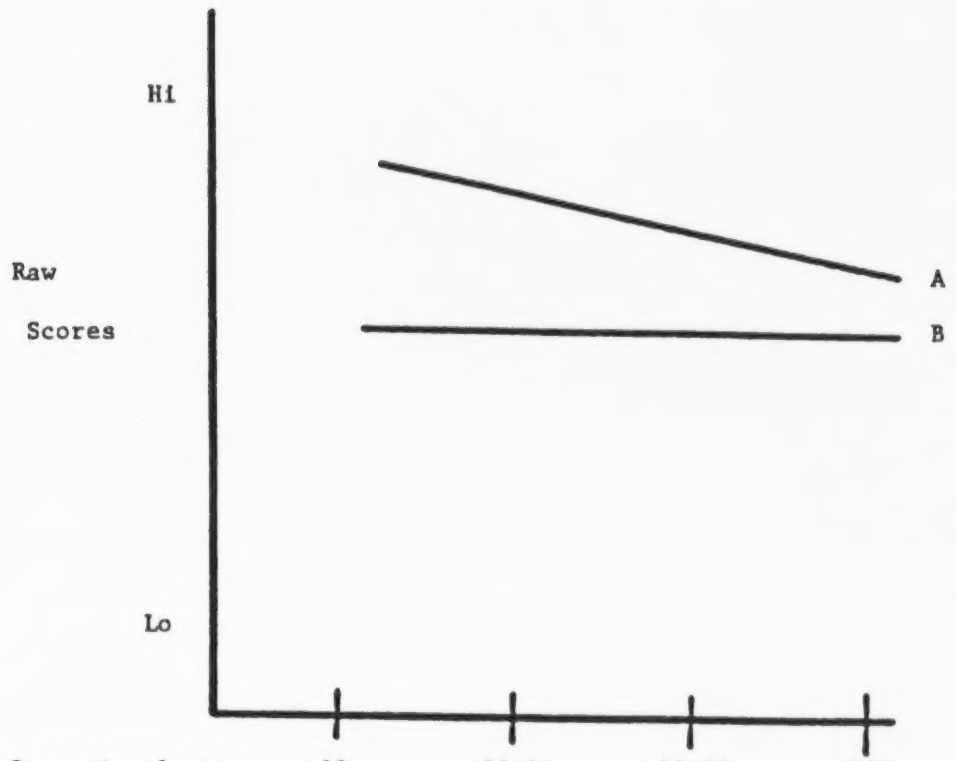
[a]=standard deviation

Table 2

Comparison of Raw Scores by Gestational Age and Neurologic Status

Test	Bayley Standardization Raw Score	Neurological Status	Gestational Age Group ≤32 weeks	33-34 weeks	35-36 weeks	≥37 weeks	p
9 month	87	Normal	88.73±1.01[a]	87.3±1.45	89.45±0.62	88.00±1.48	NS
Cognitive Raw			(n=56)	(n=70)	(n=58)	(n=52)	
Scores		Abnormal	82.08±2.23	81.65±4.27	87.67±1.04	87.43±0.95	NS
			(n=26)	(n=23)	(n=9)	(n=7)	
			p=.0348	NS	NS	NS	
9 month	40	Normal	40.20±0.51	40.94±0.37	40.38±0.42	40.82±0.45	NS
Psychomotor			(n=55)	(n=67)	(n=59)	(n=50)	
Raw Scores		Abnormal	33.52±1.43	36.65±1.92	38.33±0.97	40.29±1.41	p=0.0016
			(n=27)	(n=23)	(n=9)	(n=7)	
			p=0.0000	p=0.0004	NS	NS	

(table continues)



Gestational age (weeks)	≤ 32	33-34	35-36	≥ 37
Conceptional age (months)	9	9	9	9
Approx. Chronological age (months)	≥ 11	10.75	10	9

Figure 1

Hypothetical graphs of Bayley raw scores illustrating the effect (A) or lack of effect (B) of prematurity